PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BK-WO-1-2003	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SI 03/00023	International filing date *(day/month/year)* 14.07.2003	Priority date *(day/month/year)* 17.07.2002
International Patent Classification (IPC) or both national classification and IPC A61K47/02		
Applicant LEK PHARMACEUTICALS D.D. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.01.2004	14.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Scarponi, U Telephone No. +31 70 340-3292

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SI 03/00023

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-20 as originally filed

Claims, Numbers

1-22 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	
	No:	Claims	1-22
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO0200171 (RXKINETIX) 3 January 2002 (2002-01-03)
D2: WO0187329 (F. HOFFMANN-LA ROCHE) 22 November 2001 (2001-11-22)
D3: EP178576 (CHUGAI SEIYAKU KK, JP) 23 April 1986 (1986-04-23)
D4: EP1136068 (JCR PHARM. CO. LTD., JP) 26 September 2001 (2001-09-26)
D5: US5968899 (T. SEKINE ET AL.) 19 October 1999 (1999-10-19)

The **documents D1, D2, D4** were not cited in the international search report. Copies of the documents are appended hereto.

V.1. The present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of **present claims 1-6,10-12,15-16,19-21** is not new in the sense of **Article 33(2) PCT** in the light of the **document D1.**

In fact the document D1 discloses (the references in parentheses applying to this document) compositions comprised of a hematopoietic growth factor (notably **erythropoietin**) in an **liquid aqueous vehicle** containing a block copolymer such as **Pluronic F68 RTM**, a **polyol such as glycerol, propylene glycol or polyethylene glycol, isotonic agents** such as **phosphate buffers, sodium chloride**, sugars or **mixtures** thereof, and protein-stabilizers such as **glycerol, mannitol**, a sugar. The described compositions can optionally further contain minor amounts of a polysaccharide *(see D1, claims 1,8-16,34-35,48-52; page 7, line 27; page 11, line 8 - page 12, line 35; page 14, lines 22-32; page 16, lines 7-32; examples 1-4; Table 2).*

Analogously, the present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of **present claims 1-22** is not new in the sense of **Article 33(2) PCT** in the light of the **document D2.**

In fact the document D2 discloses (the references in parentheses applying to this document) compositions (for the **same uses** as in the present Application) comprised of an **erythropoietin** in an **aqueous isotonic solution buffered in the pH range 5.5-7.0 by a phosphate buffer** and containing up to 1% of a detergent such as **Pluronic F68 RTM**, up to 10% of a **polyol such as glycerol, mannitol, sorbitol, a sugar**, up to 0.9% of **tonicity**

agents such as **sodium chloride or sodium sulfate**, and optionally other **excipients** *(see D2, claims 1-5,8-18,22-26,41-54,56-58; page 3, line 29 - page 4, line 26; page 6, line 8 - page 7, line 20; page 22, line 4 - page 23, line 13; page 23, lines 20-30).*

Analogously, the present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of **present claims 1-7,14,17,19-21** is not new in the sense of **Article 33(2) PCT** in the light of the **document D3.**

In fact the document D3 discloses (the references in parentheses applying to this document) compositions comprised of **erythropoietin** in an **aqueous solution (buffered at pH 7.0 by a phosphate buffer** in D3, example 4) and containing an amount non exceeding 1% of additives like an **ethylene oxide-propylene oxide copolymer** (indicated as **F68** in D3, Table, and therefore conceivably being **Pluronic F68 RTM),** and like a **polyol such as** a **polyoxyethylene glycol** (polyoxyethylene glycol 4000 in D3, example 4) or dextran, together with other **excipients** such as **tonicity agents** (**sodium chloride** in D3, example 4: mannitol or sorbitol are used in the other examples of D3) *(see D3, claims; page 1, lines 10-12; page 5, lines 18-22; Table; example 4).*

In conclusion, the present application does not meet the criteria of **Article 33(1) PCT**, because the subject-matter of **present claims 1-22** is not new in the sense of **Article 33(2) PCT** in the light of all the **above mentioned documents D1 to D3.**

V.2. Furthermore, the subject-matter of present **claims 1-22** does not seem to involve an inventive step in the sense of **Article 33 (3) PCT,** and therefore the requirements of **Article 33 (1) PCT** are not met.

In fact the **documents D1 to D3** mentioned above in **paragraph V.1.** all appear to be of particular relevance as far as the inventive step is concerned (**Article 33 (3) PCT**).

These documents solve indeed the same **problem** as defined in the present Application *(see in particular the description, page 2, line 28 - page 3, line18, and the examples 2-3),* namely **the preparation of erythropoietin aqueous buffered isotonic solutions** containing an **ethylene oxide-propylene oxide poloxamer copolymer** (such as **Pluronic F68 RTM)** and a **polyol for the treatment of anemia or cancer conditions.**

Therefore - **as far as novel subject matter is concerned** - the present Application does not seem to fulfill the requirements of **Article 33 (3) PCT** over this prior art documents.

In addition, the **document D4** can be regarded as being the closest prior art to the subject-matter of present claims 1-22, and discloses (the references in parentheses applying to this document) that powders (preferably for transmucosal administration) containing **active**

peptides of any kind (e.g. erythropoietin) can be obtained from aqueous buffered isotonic solutions **stabilized** by a detergent such as a **poloxamer** (notably **Pluronic F68 RTM)** and a **soluble non-polymeric or polymeric polyol** such as a mannitol, polyvinylalcohol, hydroxypropylcellulose *(see D4, claims 1-7,10,13-19,22,25-26,29,32; paragraphs 0040, 0051, 0056, 0068, 0069, 0093)* . On the other hand, the **document D5** (the references in parentheses applying to this document) not only discloses the same kind of compositions as **document D4** (additionally containing enhancers) but also clearly states that said compositions can be useful for enteral, parenteral or transmucosal administration *(see D5, claims; column 2, line 22 - column 3, line 19; column 4, lines 4-9; column 4, lines 42-64; example 3).* Therefore, the **document D5** renders obvious even the preferred parenteral use of the claimed compositions suggested in the present Application *(see again the description, page 2, line 28 - page 3, line18, and the examples 2-3).*

In conclusion, as already stated the subject-matter of present **claims 1-22** does not seem to involve an inventive step in the sense of **Article 33 (3) PCT,** and therefore the requirements of **Article 33 (1) PCT** are not met.